REMARKS

The requisite fee for a two month extension of time can be charged to Deposit Account No. 02-1818. Any fees that may be due in connection with filing this paper or with this application during its entire pendency may be charged to Deposit Account No. 02-1818.

If a Petition for extension of time is required, this paper is to be considered such Petition, and any fee charged to Deposit Account No. 02-1818.

Claims 8-14, 58-73 and 75 are pending in this application Claim 58 is amended for clarity and consistency; claim 59 is amended in accord with claim 58. As amended, the claims render it clear that the method, which is a high throughput method, in which a plurality of oligonucleotides and host cells are screened, relies on the use of a family of oligonucleotides that are based on the sequence of a target nucleic acid molecule such that they are complementary to portions, but the complementary regions are distributed throughout the target. Hence, not necessarily all of the oligonucleotides inhibit expression of the target gene. In addition, the method includes non-bacterial cloning for the delivery, expression and amplification of the oligonucleotide family, and also employs a vector with means for providing directionality of the inserted oligonucleotides so that all are expressed.

THE REJECTION OF CLAIMS 8-14 AND 58-72 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

> Claims 9-14, and 58-73 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner urges that claim 58 remains ambiguous because it is unclear if the mRNA referred to in line 12 is the same as the "mRNA transcribed" in line 19 of this claim.

Reconsideration of the grounds for this rejection respectfully is requested in view of the amendment of claim 58.

Claim 58 is amended at what was line 19 to recite "a sequence contained in the mRNA transcribed from the sample nucleic acid sequence in the target nucleic acid molecule." This is same language in the description of the oligonucleotides at line 12, thereby properly references the antecedent therefor. Claim 58 also is amended to recite that the family of oligonucleotides used in the method are complementary to sequences throughout the target nucleic acid molecule and to render it clear that not all members of the family are required to inhibit. It is this requirement that permits screening without any conformational modeling or knowing anything about the requisite structure of an inhibitory RNA molecule. Basis for this limitiation can be found in the application, which states:

> In the disclosed invention, it is not necessary to develop conformational models of the target nucleic acids to identify regions which are particularly accessible. Such models typically are developed using computer-assisted predictions of possible thermodynamically stable secondary structures. The need for such models is avoided by creating a family of complementary ribozyme nucleotide sequences which are distributed throughout a target nucleic acid sequence.

THE REJECTION OF CLAIMS 8-14 AND 58-73 UNDER 35 U.S.C. §103(a)

Claims 8-14 and 58-73 are rejected under 35 U.S.C. §103(a) as being unpatentable over Wagner *et al.* U.S. Patent No. 6,355,415 and Draper *et al.* (U.S. Patent No. 5,496,698) in view of Gudkov *et al.* U.S. Patent No. 5,753,432. It is alleged that Wagner *et al.* teaches a method for assessing gene function in which ribozymes transiently or stably are transfected into a host cell, and the effect of ribozyme expression on the transfected cell and/or progeny derived from this cell is determined compared to controls that either are not transfected with the expression vector or are transfected with an expression vector that encodes an RNA that does not cleave the substrate RNA. In the Office Action dated November 28, 2007, the Examiner states that Draper *et al.* U.S. Patent No. 5,496,698, (at col. 1-3 and 10) teaches:

> identifying one or more members of a combinatorial ribozyme library comprising contacting a mammalian cell culture with members of the library which bind to and disrupt a transcription product and identifying host cells that exhibit phenotypic changes, whereby members of the combinatorial library are identified; wherein the identified members are used as a probe to identify nucleotide sequences; and wherein the transcription product is mRNA. . . . Draper, at col. 2, lines 47-60, states: "[A]pplicant provides an in vivo system for selection of ribozymes targeted to a defined RNA target. The system allows many steps in a selection process for desired ribozymes to be bypassed. In this system, a population of ribozymes having different substrate binding arms (and thus active at different RNA sequences) is introduced into a population of cells including a target RNA molecule. The cells are designed such that only those cells including a useful ribozyme will provide a detectable signal. In this way, a large population of randomly or nonrandomly formed ribozyme molecules may be tested in an environment which is close to the true environment in which the ribozyme might be utilized as a therapeutic agent."

The Examiner states that Wagner *et al.* and Draper *et al.* do not teach that their methods do not comprise intervening bacterial cloning steps nor that the method does not comprise conformational modeling of mRNA transcribed from the target nucleic acid molecule. The Examiner urges, however, that "the prior art discloses methods for assigning function to a transcription product of a target nucleic acid without the need for intervening bacterial cloning steps and conformational modeling" and cites Gudkov *et al.*, presumably for this proposition. The Examiner states that Gudkov *et al.* provides methods for designing a retroviral library of nucleic acid fragments to be delivered to eukaryotic cells to test or

determine the ability of these nucleic acid fragments to function as genetic suppressor elements (GSE) (see col. 10-12). The Examiner states that the methods of Gudkov *et al.* "essentially comprise methods for identifying gene function since the ability of the putative nucleic acid molecules to function as a GSE is unknown prior to testing." The Examiner also states that the methods of Gudkov *et al.* does not recite intervening bacterial cloning steps or conformational modeling. The Examiner, thus, appears to be urging that, because Gudkov *et al.* does not explicitly teach an intervening bacterial cloning step, the absence of such teaching is a teaching of a method of assigning a function in the absence of intervening cloning steps.

In the Office Action dated September 3, 2008, the Examiner concludes that it would have been obvious to one of ordinary skill in the art to have combined:

> the teachings of Wagner et al. and Draper et al. with the teachings of Gudkov et al. in the design of the instant invention. One of ordinary skill in the art would have been motivated to make this modification since Wagner et al. and Draper et al. expressly state that their disclosed methods for determining gene function encompass wherein the transfection method comprises the use of retroviral vectors, and the teachings of Gudkov et al. are specifically designed to deliver nucleic acid to cells using retroviral vectors with the express purpose of determining their ability to alter a phenotype of the transfected cells.

In particular, the Examiner states:

> In regards to Applicant's arguments that none of the cited references teaches or suggests a high throughput method of assigning a gene function nor elimination of any intervening bacterial cloning steps, since it is clear that the prior art teaches method for using antiense/ribozymes to inhibit gene function, and thus observe phenotype associated with this inhibition, it would have been obvious to the ordinary skilled artisan to design a system that would provide this method in a faster more efficient process, i.e. in a "high throughput" method. Moreover, in regards to the non-bacterial cloning step,this limitation merely eliminates a processing step, which one of ordinary skill in the art would have increased the productivity of the method, see MPEP § 2143 which recites: "[T]he Courts have made clear that the teaching, suggestion, or motivation test is flexible and an explicit suggestion to combine the prior art is not necessary. The motivation to combine may be implicit and may be found in the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved. Id. at 1366, 80 USPQ2d at 1649. "[A]n implicit motivation to combine exists not only when a suggestion may be gleaned from the prior art as a whole, but when the improvement' is technology-independent and the combination of references results in a product or process that is more desirable, for example because it is stronger, cheaper, cleaner, faster. lighter. smaller, more durable. or more efficient. Because the desire to enhance commercial opportunities by improving a product or process is universal-and even common-sensical-we have held that there exists in these situations a motivation to combine prior art references even absent any hint of suggestion in the references themselves. In such situations, the proper question is whether the ordinary artisan possesses knowledge and skills rendering him capable of combining the prior art references." Id. at 1368, 80 USPQ2d at 1651."

This rejection respectfully is traversed. Before discussing the rejection in detail, Applicant addresses the Examiner's contention that "one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references." Applicant has not argued non-obviousness by attacking the references individually. In this instance, the combination of teachings of the references fails to result in the instantly claimed methods. The structure of the argument as set forth in the previous responses and below is to first discuss the deficiencies in the teachings of each reference and then to combine the teachings of the references and, to thereby, identify the teachings that are missing from the combination. In this instance, as discussed in more detail below, the combination of references fails to teach or suggest a high throughput method for assigning a function to a gene of unknown function by employing a library of a family of oligonucleotides based on a target gene, where sequences of the mRNA to which the transcription product of the oligonucleotide family members are complemenary are distributed throughout the target nucleic acid molecule such that among the members of the library are those that inhibit function of the target. This does not require knowledge of the conformation or structure of the target gene, and as a result does not require any intermediate bacterial cloning steps nor any design steps. The use of the library of the family of oligonucleotides provides the oligonucleotide that will inhibit expression. As a result the method is amenable to a high throughput format. In addition, the method specifically requires that the oligonucleotides are provided in vectors that include means for directionality so that the double-stranded DNA is ligated into the delivery vector in the correct orientation for expression. The combination of teachings references does not teach or suggest such method.

The Examiner appears to urge that because Wagner *et al.* teaches a method of assigning function, Draper *et al.* teaches a method for selecting ribozymes and Gudov *et al.* provides a method that those may not employ intervening bacterial cloning steps, that the ordinarily skilled artisan would read Wagner *et al.* and Draper *et al.* and Gudov *et al*, and conclude somehow that the method of Wagner should somehow be modified to employ a library of oligonucleotides as claimed and perform the method in a high throughput format using double-stranded vectors as required by the instant claims.

As discussed below, the silence of Gudov *et al.* regarding high throughput and use of an oligonucleotide is **not** a teaching that would result in the instantly claimed methods. None of the references even teaches or suggests that there is a deficiency in the method of Wagner

et al. or Wagner *et al.* and Draper *et al.* nor is there a suggestion for performing any method in high throughput format and using a family of oligonucleotides designed as recited in the claims.

Before proceeding to the discussion below, Applicant comments on the Examiner's statement:

> A]n implicit motivation to combine exists not only when a suggestion may be gleaned from the prior art as a whole, but when the improvement' is technology-independent and the combination of references results in a product or process that is more desirable, for example because it is stronger, cheaper, cleaner, faster. lighter. smaller, more durable. or more efficient. Because the desire to enhance commercial opportunities by improving a product or process is universal-and even common-sensical-we have held that there exists in these situations a motivation to combine prior art references even absent any hint of suggestion in the references themselves. In such situations, the proper question is whether the ordinary artisan possesses knowledge and skills rendering him capable of combining the prior art references." Id. at 1368, 80 USPQ2d at 1651."

The cited case law is directed to the finding of motivation to combine references from the desire for improvement of a process, where the combination of references results in the claimed process. Such is **not** the issue here. In the instant case, Applicant is not necessarily questioning the motivation to combine the references, but points out that the combination of teachings of the references **does not** result in the claimed method. None of the cited references, singly or in combination, teaches or suggests a high throughput method for assigning gene function. The Examiner cannot cite case law for the proposition that the desire for an improved process can provide motivation to combine references that result in the process to support the contention that such desire can be used to modify the combined teachings to produce the claimed method in the absence of any teaching or suggestion in the cited art for such modification. The mere fact that prior art may be modified to produce the claimed product does not make the modification obvious unless the prior art suggests the desirability of the modification. In re Fritch, 23 USPQ2d 1780 (Fed. Cir. 1992); see, also, In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963). Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. Ex parte Gerlach, 212 USPQ 471 (Bd. APP. 1980).

The discussion below, describes the teachings of each reference separately, describing the deficiencies of each reference, and then in the section headed "Analysis," discusses the deficiencies in the **combination** of teachings of the cited references. As the case law discussion below renders clear, for claimed subject matter to be obvious, the combination of

teachings of the references must result in what is claimed. In this instance, the combination of teachings of the references is deficient.

Relevant Law

To establish prima facie obviousness under 35 U.S.C. §103, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). This principle of U.S. law regarding obviousness was not altered by the recent Supreme Court holding in KSR International Co. v. Teleflex Inc., 127 S.Ct. 1727, 82 USPQ2d 1385 (2007). In KSR, the Supreme Court stated that "Section 103 forbids issuance of a patent when 'the differences between the subject matter sought to be patented and the prior art are such the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.'" KSR Int'l Co. v. Teleflex Inc., 127 S.Ct. 1727, 1734, 82 USPQ2d 1385, 1391 (2007).

The mere fact that prior art may be modified to produce the claimed product does not make the modification obvious unless the prior art suggests the desirability of the modification. In re Fritch, 23 USPQ2d 1780 (Fed. Cir. 1992); see, also, In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963). Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. Ex parte Gerlach, 212 USPQ 471 (Bd. APP. 1980).

The question of obviousness is resolved on the basis of underlying factual determinations including (1) the scope and content of the prior art, (2) any differences between the claimed subject matter and the prior art, (3) the level of skill in the art. Graham v. John Deere Co., 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966). See also KSR, 127 S.Ct. at 1734, 82 USPQ2d at 1391 ("While the sequence of these questions might be reordered in any particular case, the [Graham] factors continue to define the inquiry that controls.") The Court in Graham noted that evidence of secondary considerations, such as commercial success, long felt but unsolved needs, failure of others, etc., "might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." 383 U.S. at 18, 148 USPQ at 467. Furthermore, the Court in KSR took the opportunity to reiterate a second long-standing principle of U.S. law: that a holding of obviousness requires the fact finder (here, the Examiner), to make explicit the analysis supporting a rejection under 35 U.S.C. 103, stating that "rejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational

underpinning to support the legal conclusion of obviousness. Id. at 1740-41, 82 USPQ2d at 1396 (citing In re Kahn, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006)).

While the KSR Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. KSR, 127 S. Ct. at 1731. The Court indicated that there is no necessary inconsistency between the idea underlying the TSM test and the Graham analysis." *Id.* As long as the test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight" to an obviousness inquiry. *Id.* "Thus, in cases involving new compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound." Takeda v. Alphapharm

THE CLAIMS

Independent Claim 58 is directed to **high-throughput method** of assigning a function associated with a product coded for by a sample nucleic acid sequence in a target nucleic acid molecule that includes, **without any intervening bacterial cloning steps** and without any conformational modeling of mRNA transcribed from the sample nucleic acid sequence in the target nucleic acid molecule: a) delivering into, amplifying and expressing a plurality of members of an oligonucleotide family as individual transcription products in a plurality of recombinant non-bacterial host cells; and, b) in the resulting host cells, comparing the phenotypes of the resulting host cells to phenotypes of control cells to identify changes in phenotype to thereby assign a function associated with the product encoded by the sample nucleic acid sequence in the target nucleic acid molecule, wherein control cells are untransfected host cells, whereby changes in phenotype can be assigned by comparison of the transfected host cell, and the un-transfected host cell. The product encoded by the sample nucleic acid sequence is associated with at least one phenotypic property of a host cell containing the mRNA.

The oligonucleotide family comprises a plurality of nucleic acid molecules; each member of the oligonucleotide family: (1) encodes a transcription product containing a sequence that is complementary to a sequence contained in the mRNA transcribed from the sample nucleic acid sequence in the target nucleic acid molecule; (2) the sequences of the mRNA to which the transcription product of the family members are complementary are

distributed throughout the target nucleic acid molecule; (3) the coding sequence for each individual transcription product encodes an antisense nucleic acid that binds to the mRNA transcribed from the sample nucleic acid sequence in the target nucleic acid molecule; and (4) the members of the oligonucleotide family are introduced into expression vectors, which are introduced into the host cells.

The expression vectors in which the oligonucleotide family members are introduced, are double-stranded DNA vectors for expression in non-bacterial host cells; that contain: a) a sense strand and an antisense strand, where the sense strand encodes a transcription product that is complementary to and binds to an mRNA sequence transcribed from the sample nucleic acid sequence in the target nucleic molecule; and b) means for determining directionality of expression so that the double-stranded DNA is ligated into the delivery vector in the correct orientation for expression.

Dependent claims further specify types of function, whether phenotypic change is monitored directly, types of sample nucleic acids, numbers of oligonucleotide family members, and types of high-throughput formats. Dependent claims 73 and 74 specify that the oligonucleotide family is a ribozyme family and claim 74 further specifies how the ribozyme oligonucleotide library is designed.

Differences Between the Claims and the Teachings of the Cited References

Wagner *et al.*

Wagner *et al.* is directed to the use of ribozymes that specifically cleave a target nucleic acid sequence of interest in a host cell, thus inhibiting expression of the product encoded by the target nucleic acid and altering the phenotype of the host cell. The altered phenotype is then analyzed to identify the function of the product encoded by the target nucleic acid sequence of interest. Wagner *et al.* teaches that this method may be used to study genes that are homologous to mammalian, including human, genes in suitable model systems such as zebrafish. The function of the homologous human or mammalian gene can then be deduced by identifying the function of the corresponding gene in zebrafish.

The methods of Wagner *et al.* employ ribozymes that are specifically designed to bind to and cleave the target nucleic acid. Typically, one ribozyme in used in the methods (see, e.g., col. 2, line 62 to col. 3, line 2, and col. 15, lines 1-6). This ribozyme binds to and cleaves the target nucleic acid, effecting a change in phenotype of the cell. As taught by Wagner *et al*, "it is desirable to express a sufficient amount of ribozyme such that substantially all the substrate RNA is cleaved." (col. 22, line 34). Further, "any level of

ribozyme expression is deemed to be within the scope of the methods disclosed herein, so long as the expressed ribozyme results in a reduced level of substrate RNA relative to the control." (col. 22, lines 40-44). To increase the efficiency of the ribozyme, methods of increasing the expression level of the ribozyme can be employed (col. 23, line 1 to col. 24, line 44). In some instances, to increase the expression levels of ribozyme in the host cell, more than one ribozyme is expressed (col. 23, lines 44-52). Each ribozyme binds **and** cleaves the target nucleic acid. Wagner *et al.* exemplifies the methods by demonstrating the computer modeling and identification of 3 accessible sites of mRNA transcribed from zebrafish *ntl* *c*DNA, then the design of 3 ribozymes that bind to and cleave the 3 accessible sites and their use to identify the function of the *ntl* gene (*see* Example 1 beginning at col. 31). Thus, for the methods of Wagner *et al.* to be effective, even where two or three ribozymes are used, the expressed ribozyme **must** bind **and** cleave the target nucleic acid. The method **does not** employ a family of ribozymes (or any oligonucleotides) whose transcription products are complementary to mRNA sequences that are distributed throughout the target nucleic acid molecule. The methods of Wagner *et al.* require that each expressed ribozyme bind and cleave a target. Hence Wagner does not employ a family of oligonucleotides that are not all designed to bind and cleave (or bind and inhibit expression) as used in the instantly claimed methods.

There is no suggestion or teaching in Wagner *et al.* of any high-throughput methods of assigning function to a product encoded by a target nucleic acid molecule by constructing an oligonucleotide family library based on complementary sequences **distributed** throughout the mRNA transcribed from sample nucleic acid in the target molecule of interest. Wagner *et al.* does not teach or suggest constructing an oligonucleotide family library based on complementary sequences **distributed** throughout the mRNA. Wagner *et al.* teaches the design and use of ribozyme molecules, each of which **must bind and cleave** the target mRNA. Preferably, this is achieved by studying the secondary structure of the mRNA for accessible sites (col. 18 line 40). Such methods are **not** amenable to a high throughput format. Several modifications, such as those present in the instant methods, are required to make the methods of Wagner *et al.* amenable to a high throughput format. None of these modifications, however, are taught or suggested by Wagner *et al.* (nor as discussed below, supplied by the secondary references). Indeed, there is no suggestion in Wagner *et al.* to make any modification to its methods, because no deficiency in the methods is identified (either by Wagner *et al.*, nor any cited reference). Wagner *et al.* neither teaches nor suggests

that it would be desirable to modify the methods to be amenable to a high throughput format, nor what these modifications need be. For the purposes of Wagner *et al.*, the use of, for example, one, two or three ribozyme molecules, each of which must **bind and cleave** the target mRNA, is sufficient to practice the methods described therein. There is no suggestion, nor is there any desirability, to use a library of a family of oligonucleotides. Further, there is no suggestion in Wagner *et al.* to modify the methods to avoid the use of intervening bacterial cloning steps.

In contrast, the instant method provides a high throughput method of assigning a function associated with a product coded for by a sample nucleic acid sequence in a target nucleic acid molecule. Unlike Wagner *et al.,* this method avoids the necessity of having every ribozyme bind **and cleave** the target nucleic acid. Further, to ensure that the methods are amenable to a high throughput format, there are no intervening bacterial cloning steps in the instant method. In the instant method, therefore, an oligonucleotide family is designed based on sequences that are complementary to sequences throughout the target nucleic acid. The plurality of oligonucleotide family molecules containing sequences so designed are then introduced into a plurality of host cells, expressed as individual transcription products in the host cells, and the host cells are assessed in high-throughput format for inhibition of expression of the target sequence of interest. This is all performed without any intervening bacterial cloning steps. Host cells that show inhibition of expression of the target are identified as containing oligonucleotide family members whose transcription products bind to the mRNA molecule transcribed from the target nucleic acid molecule for whose product a function is assigned.

In the instantly claimed methods, the oligonucleotide family contains a plurality of putative antisense or ribozyme sequences, and the high-throughput method "screens" for the ones that effectively bind to and/or cleave the target mRNA. Thus, using the instant methods, it is not necessary to specifically design ribozymes that bind **and** cleave the target nucleic acid. Rather, a large number of complementary sequences, regardless of whether their transcription products are effective antisense or ribozyme molecules, are used to make up the oligonucleotide family library. This large number of resulting transcription products ensures that at least one will inhibit production of the product of the target nucleic acid, resulting in a change in phenotype. Thus, although not all of the transcription products inhibits production of the product of the mRNA, the method is still effective. Because the oligonucleotide family is designed based on sequences that are complementary to sequences throughout the target

nucleic acid, and requires no further design, such as conformational modeling of the target nucleic acid, or testing to ensure that each one encodes an effective antisense or ribozyme molecule, the methods can be practiced in a high-throughput format. Further, the fact that the instant methods do not include any intervening bacterial cloning steps also facilitates it's use in a high throughput format. None of these elements is taught by Wagner *at al.*

Thus Wagner *et al.* is deficient in failing to teach or suggest several essential elements of the instantly claimed method. For example, Wagner *et al.* fails to teach or suggest a **high-throughput method** of assigning a function associated with a product coded for encoded by a sample nucleic acid sequence in a target nucleic acid molecule; fails to teach or suggest the use of an oligonucleotide family based on sequences distributed throughout the mRNA encoded by the target; and fails to teach or suggest a method that does **not include any intervening bacterial cloning steps**.

The secondary references, singly or in any combination, do no cure these deficiences.

Draper *et al.*

Draper *et al.* teaches a method for *in vivo* selection of a ribozyme active at a defined RNA target. According to Draper *et al.*, in its method, a population of ribozymes having different substrate binding arms is introduced into a population of cells that express a target RNA molecule. The population of ribozymes contains ribozymes that differ in either or both ribozyme substrate binding arms whose sequence is randomized is "quasi-"randomized. Only cells that contain a ribozyme of desired specificity will survive or provide a detectable signal for selection of ribozymes of a desired specificity.

Hence Draper *et al.* provides a **method for identifying ribozymes** with a particular activity by screening a library of ribozymes with substrate binding arms that contain random or quasi-random sequences in order to produce and select ribozymes of a desired specificity. A library of ribozymes is introduced into cells and their activity is screened to identify ribozymes.

Draper *et al.*, does **not** provide a method for assigning a function to a gene product by inhibiting expression of the gene product using a family of oligonucleotides whose sequences are based on a sample sequence in a target. In the instantly claimed methods, the family of oligonucleotides, whose sequence is based on the target, is used, not to identify a particular ribozyme, but to inhibit expression of a gene without the requirement or need to ensure that each and every oligonucleotide does so. This is performed in order to assign a function to the gene product.

Thus Draper *et al.* is of no relevance to the instantly claimed methods, and it does not cure any of the above-noted deficiencies in the teachings of Wagner *et al.*

Draper *et al.* does not teach or suggest any method of assigning function to a product encoded by a target nucleic acid molecule by constructing an oligonucleotide family library based on complementary sequences throughout the mRNA transcribed from sample nucleic acid in the target molecule of interest. Draper *et al.* does not teach or suggest constructing an oligonucleotide family library based on complementary sequences throughout the mRNA. In fact, Draper *et al.,* specifically states that "it is not necessary to know either the mRNA sequence of the target mRNA...to select for active ribozyme constructs in this cellular system" (col. 1, line 29). Nor does Draper *et al.* teach or suggest a high throughput method. Draper *et al.* provides no teaching or suggestion that would have led one of ordinary skill in the art to have modified the methods of Wagner *et al.* to be amenable to a high throughput format. For example, there is no teaching or suggestion in Draper *et al.* of **a high throughput** method for assigning a function to a gene product that **involves no bacterial cloning steps**. Thus, Draper *et al.* does not cure the deficiencies in the teaching of Wagner *et al.* Gudov *et al.* fails to cure the deficiencies in the combined teachings of Wagner *et al.* and Draper *et al.*

Gudkov *et al.*

Gudkov *et al.* is directed to the identification of genetic suppressor elements (GSEs). In the method of Gudkov *et al.*, **a random expression** library is constructed based on cDNA derived from normal cells. The random library itself is then screened for inserts containing GSEs that render cells immortalized, tumorigenic or morphologically transformed. In all instances, the presence of a GSE sequence is identified by the transformation of the cell. The identity of the gene to which the GSE binds, resulting in a transformed phenotype, is unknown. Thus, it is respectfully submitted that, in contrast to the Examiner's assertions on page 8 of the Office Action dated September 3, 2008, this method **can not** assign a function to a gene product if that gene product is known. Rather, the methods identify a new GSE. In some instances, the identified GSEs are sequenced and then used to screen full length cDNA molecules and identify the corresponding genes. This process, however, is performed with single, isolated, known GSEs (col. 16. line 28), the isolation of which requires cloning.

Gudkov *et al.* does not teach or suggest any method of **assigning a function to a product** encoded by a known sequence of interest. Gudkov *et al.* identifies heretofore unknown sequences as being GSEs. Gudkov *et al.* does not teach or suggest use of, or preparation of, an oligonucleotide family library based on complementary sequences

throughout the mRNA transcribed from the target molecule of interest, nor does Gudkov *et al.* teach or suggest a high throughput method. Gudkov *et al.* does not appear to have any relevance to the instantly claimed methods.

The Examiner states that Gudov *et al.* is "essentially" a method for assigning a function and thus, is combinable with Wagner *et al.*, and Draper *et al.*. While Applicant disagrees with this assertion for the reasons discussed above, assuminig *arguendo* that Gudov *et al.* could be so-interpreted, its silence regarding the use of intervening bacterial cloning steps **cannot** be construed as an affirmative teaching that the the methods of Wagner *et al.* and/or Draper *et al.*, singly or in combination, can be modified and rendered high throughput. Even if it did suggest that performing the methods of Wagner *et al.* and/or Draper *et al.* without any intervening bacterial cloning steps is desirable, Gudov *et al.* fails to teach or suggest a high throughput method that relies on a family of oligonucleotides based on sequences distributed throughout the mRNA encoded by the target, nor does Gudov *et al.*, or Wagner *et al.*, or Draper *et al.*, teach or suggest introducing such an oligonucleotide family into non-bacterial expression vectors designed so that the double-stranded DNA is ligated into the delivery vector in the correct orientation for expression.

As discussed, the instant claims are directed to a method of assigning a function to a known target gene of interest. The target sequence is known, but its function is unknown. The oligonucleotide family used in the instant methods is designed based on this known target sequence (*i.e.*, identifying sequences that are complementary to the known target sequence). Gudkov *et al.*, however, employs a **random library of all cDNA**, known and unknown sequences, derived from a normal cell. This random library itself is then introduced into cells to identify the presence of a GSE sequence in the library, **not to assign a function to a gene product.** Hence, this method is completely different from the instantly claimed method. Further, there is no suggestion or teaching in Gudkov *et al.*, of a high throughput method for assigning a function to a gene product that involves no bacterial cloning steps.

Gudkov *et al.*, teaches virtually none of the elements of the instantly claimed methods. Thus, Gudkov *et al.* does not cure the deficiencies in the teachings of Wagner *et al.* and Draper *et al.*

ANALYSIS

The combination of teachings of Wagner *et al.*, Draper *et al.*, and Gudov *et al.*, does not result in the instantly claimed methods.

It respectfully is submitted that the Examiner has failed to set forth a case of *prima facie* obviousness because the combination of teachings of the cited references **does not** result in the instantly claimed methods. Among the elements of the instantly claimed methods that are not taught are suggested by any of the cited references, singly or in combination, are: (1) a high throughput method for assigning a function; (2) a method without intervening bacterial cloning steps; (3) a method that employs a family of oligonucleotides based on complementary sequences distributed throughout the mRNA transcribed from sample nucleic acid in the target molecule of interest so that each oligonucleotide is not required to bind and inhibit; (4) use of double stranded DNA vectorst include means for directionality so that the oligonucleotide is ligated into the delivery vector in the correct orientation for expression.

As discussed above, Wagner *et al.* fails to teach any of these elements Wagner *et al.*, does not teach or suggest constructing an oligonucleotide family library based on complementary sequences distributed throughout the mRNA. Wagner *et al.*, teaches the design and use of ribozyme molecules, each of which must bind **and** cleave the target. The methods taught in Wagner *et al.*, require that the ribozymes bind and cleave the target nucleic acid for the method to function as described. Typically, just one ribozyme is used. In some instances, to increase efficiency of the ribozyme, expression levels are increased by introducing more than one ribozyme, such as three ribozymes, but Wagner *et al.* does not suggest use of a family of oligonucleotides, where not all of them necessarily bind and inhibit. As stated in Wagner *et al.*, however, "any level of ribozyme expression is deemed to be within the scope of the methods disclosed herein, so long as the expressed ribozyme results in a reduced level of substrate RNA relative to the control." (col. 22, lines 40-44). Thus, Wagner *et al.* teaches that each ribozyme must be designed so that it is effective at cleaving the mRNA. This is time-consuming and not amenable to a high-throughput screen.

In contrast, the oligonucleotide family library used in the instant high-throughput method is based only on complementary distributed sequences throughout the target mRNA and does not require that all members of the family encode a transcription product that inhibits the product of the mRNA transcribed from the target nucleic acid. Only one need be effective for the instant methods to inhibit expression of a target gene.

Wagner *et al.* does not does not teach or suggest a high-throughput method of assigning a function to a product encoded by a target nucleic acid of interest nor a method that does not involve intervening cloning steps, nor a method in which the oligonucleotides are expressed in a vector that includes means for directionality.

Further, the instant methods are performed without the use of intervening bacterial cloning steps, an element also not taught by Wagner *et al.* This element, with the use of the oligonucleotide family, facilitates the use of a high-throughput format in the instant methods. There is no suggestion in Wagner *et al.* to make **any** modification to the methods taught therein, because no deficiency in the methods is identified. Wagner *et al.* neither teaches nor suggests that it would be desirable or advantageous to modify the methods to be amenable to a high throughput format, nor what these modifications need be. There is no suggestion, nor is there any desirability, to use a library of oligonucleotides, because each of the ribozymes in the Wagner *et al.* method is designed to cleave the target nucleic acid. Further, there is no suggestion in Wagner *et al.* to modify the methods to avoid the use of intervening bacterial cloning steps, because using intervening bacterial cloning steps with the limited number of required ribozymes in the methods of Wagner *et al.* is not burdensome.

Draper *et al.* **does not** cure these deficiencies. Draper *et al.* provides a method for identifying and selecting ribozymes, not for assigning a gene function. Draper *et al.* does not teach or suggest constructing an oligonucleotide family library based on complementary sequences throughout the mRNA. There is no suggestion in Draper *et al.* for replacing the fully effective ribozymes used in Wagner *et al.* with an oligonucleotide family library. Further, Draper *et al.,* does not teach or suggest a high throughput method for assigning a function to a gene product that involves no bacterial cloning steps, nor does Draper *et al.* teach that the methods taught therein should be modified to a high throughput method for assigning a function to a gene product that involves no bacterial cloning steps. In Draper *et al.* the method is for identification of ribozymes, not for assigning gene function, which is a very different purpose for which Wagner *et al.* models its ribozymes. In addition to the fact that there would be no motivation for one of skill in the art to combine the two, their combination does not result in the instant methods.

Gudkov *et al.* does not cure the deficiencies in the teachings of Wagner *et al.* and/or Draper *et al.* Gudkov *et al.*, which identifies new GSEs, is not directed to a method of assigning function to a product encoded by a known sequence of interest. Gudkov *et al.* employs a random library of fragments derived from cDNA from normal cells, from which

new GSEs are identified. Gudkov *et al.* does not appear to have any relevance to the instantly claimed methods. Gudkov *et al.* does not describe any method for assigning function to a transcription product of a target nucleic acid without the need for intervening bacterial cloning steps.

The instant method utilizes a plurality of complementary sequences from an oligonucleotide family in a plurality of host cells, then uses the method to select for those that effectively bind to and/or cleave the target mRNA by identifying those host cells that show inhibition of expression of a product of the mRNA. This renders the method amenable to high-throughput format by avoiding the need to first identify one or more ribozyme (or antisense) molecules that effectively inhibit expression of a product of the mRNA. Further, the instant methods have no intervening bacterial cloning steps. These elements render the instant methods amendable to high through-put format. None of the cited references, singly or in combination, teaches or suggest the instant methods,

There is no teaching or suggestion in either Wagner *et al.*. Draper *et al.*, or Gudkov *et al.*, singly or in any combination of a high throughput method for assigning a function to a product encoded by a known target sequence. The only reference that assesses gene function is that of Wagner *et al.*, but Wagner *et al.* fails to teach or suggest a high-throughput method in which there are no intervening bacterial cloning steps as well as the other elements noted above. There is no suggestion in Wagner *et al.* of modifying its methods to be amenable to a high-throughput format, such as by using a family of oligonucleotides and eliminating any intervening bacterial cloning steps. Further, there is no suggestion that doing so would be advantageous or desirable.

Draper *et al.* is directed to a screening method for identifying and selecting ribozymes. It is not directed to a method for assigning a function to a product encoded by a known target sequence. Draper *et al.* provides no suggestion for modifying the methods of Wagner *et al.* to be amenable to high through-put format by using a family of oligonucleotides or eliminating any intervening bacterial cloning steps or using the double-stranded DNA vectors as claimed.

Regarding Draper *et al.*, the Examiner states:

> In regards to Draper et al., Applicants argued that Draper et al. does not provide for a method for assigning a function to a gene product by inhibiting the expression of the gene product using a family of oligonucleotides whose sequences are based on a sample in the target. Again, Applicants are attempting to show nonobviousness by attacking Draper et al. individually. Contrary to Applicant's assertions, the Draper et al. reference is provided to set forth what

> was known in the prior art regarding the design and use of a combinatorial library of ribozyme molecules, particularly wherein a population of ribozymes having different substrate binding arms, and targeting the same mRNA, is introduced into a population of cells including a target RNA molecule. The cells are designed such that only those cells including a useful ribozyme will provide a detectable signal. Moreover, contrary to Applicant's assertions, due to the teachings of Draper et al. which define a large scale screen of a plurality of ribozymes in a population of cells, absent evidence to the contrary, the teachings of Draper et al. are amenable to a high throughput process for assigning an activity to a target mRNA in a cell, namely inhibition.

Draper *et al.*, however, does not teach or suggest replacing the ribozymes in the methods of Wagner *et al.*, which ribozymes must bind to and cleave the target, with a family of olignucleotides that are complementary to sequences distributed throughout the target in a format in which it is not necessary for all members of the family to bind and inhibit.

Gudkov *et al.* does not cure these deficiencies. Gudkov *et al.* teaches identification of heretofore unknown sequences possessing a certain property (GSE) from a random cDNA library. At best, Gudkov *et al.* teaches a high-throughput method of identifying GSEs, a process that utilizes a random library of fragments derived from cDNA from normal cells. Thus, the methods of Gudkov *et al.* are in no way relevant to the instant methods, nor do they teach or suggest a high throughput method for assigning a function to a product encoded by a known target sequence, wherein the method has no intervening bacterial cloning steps. Further, it is respectfully submitted that, contrary to the Examiner's assertions, the mere fact that the methods in Gudknov *et al.* use retroviral vectors is not motivation for one of ordinary skill in the art to use them in the method of Wagner *et al.* and/or Draper *et* al. The fact that Gudknov *et al.* use retroviral vectors and Wagner *et al.* and Draper *et al.* state that their methods also can use retroviral vectors, is essentially the only similarity between the references. Wagner *et al.* teaches a method for assessing gene function, Draper *et al.* teaches a method for identifying ribozymes, and Gudkov *et al.* teaches a method for identifying GSEs.

Thus, the combination of teachings of Wagner *et al.*, Draper *et* al. and Gudov *et al.* , singly or in any combination thereof, does not thereof results in the instantly claimed methods. The combination of teachings fails to teach or suggest any and all of the following elements: (1) a high throughput method for assigning a function; (2) a method without intervening bacterial cloning steps; (3) a method that employs a family of oligonucleotides based on complementary sequences distributed throughout the mRNA transcribed from sample nucleic acid in the target molecule of interest so that each oligonucleotide is not required to bind and inhibit; (4) use of double stranded DNA vectorst include means for

directionality so that the oligonucleotide is ligated into the delivery vector in the correct orientation for expression. Thus, the combination of teachings does not result in the instantly claimed methods.

Furthermore, the combination of teachings of the cited references does not provide any suggestion for modifying the methods of Wagner *et al.*, singly or in combination with the secondary references, to arrive at the instantly claimed methods, nor that such modification would be advantageous or desirable. None of the references teaches or suggests that modification of the method of Wagner *et al.* to be in high throughput format is desirable, none suggests replacing the ribozymes used in Wagner *et al.* such that not all bind and cleave, nor any of the other elements noted to be absent. As discussed above, the mere fact that prior art may be modified to produce that which is claimed does not make the modification obvious unless the prior art suggests the desirability of the modification. In re Fritch, 23 USPQ2d 1780 (Fed. Cir. 1992); see, also, In re Papesch, 315 F.2d 381, 137 USPQ. 43 (CCPA 1963).

As discussed above, the Examiner's reliance on a case law that suggests that motivation to combine references can be found in the general desire to make a process more efficient, is not applicable where the combination of references, whether properly combinable or not, **does not result** in the claimed methods. Such motiavation, cannot substitute for the failure of the combination of references to teach essential elements of the claimed methods. In this instance, none of the cited references teaches or suggests or mentions the high throughput, nor provides any teaching or suggestion for achieving such method, nor provides any teaching or suggestion for modifying the methods of the cited references. Under all standards of obviousness, the combination of teachings of cited references must result in the claimed subject matter. There must be some motivation or suggestion to that which an applicant has done (see In re Fritch; see also, PharmaStem Therapeutics. Inc. v. ViaCell. Inc., 491 F.3d 1342 (Fed. Cir. 2007), where the Federal Circuit stated that:

> an invention would not be invalid for obviousness if the inventor would have been motivated to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. Likewise, an invention would not be deemed obvious if all that was suggested was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

The cited references singly or in any combination do not result in the the instantly claimed methods. The mere fact that one of ordinary skill in the art could have decided to perform the method of Wagner *et al.* does not render such format obvious in the absence of some teaching or suggestion any cited reference that such is desirable. Further, the mere fact that it might be possible to modify the method of Wagner *et al.* does not ensure or teach or suggest that such modification would be achieved as claimed in the instant application. None of the cited references teaches or suggests any methods that employs a family of oligonucleotides as required by the instantly claimed methods, nor requires that there are no intervening bacterial cloning steps, or requires the use of the double-stranded vectors.

Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

* * *

In view of the above amendments and remarks, reconsideration and allowance of the application respectfully are requested.

Respectfully submitted,

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